

# Intravenous Immune Globulin: Practical Considerations for Transfusion Medicine Services

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BBANYS  
June 4, 2009

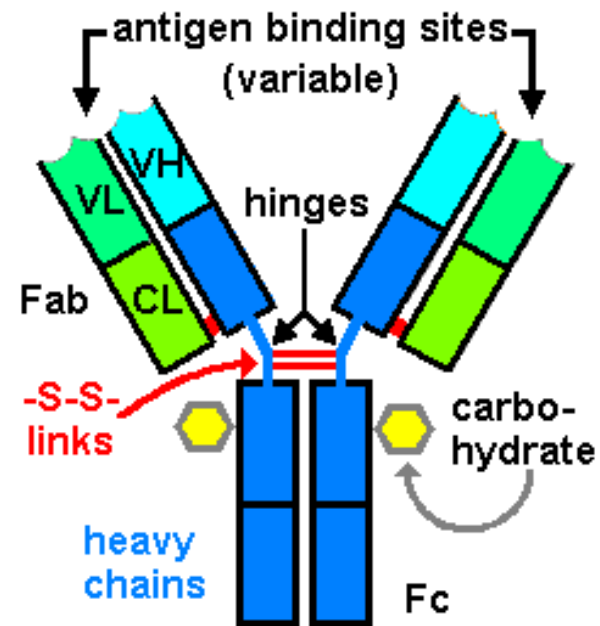
## Objectives:

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- **General overview of IVIG**
- **Indications and Use**
- **Mechanisms of action**
- **Adverse Events**

# Structure of Ig G

- **Fab- antibody specificity and antigen binding**
- **Fc portion**
  - Determines class and subclass (isotype)
  - Interacts with neutrophils and macrophages
  - Activates complement
  - Flexible hinge portion is responsible for avidity



Immunoglobulin G (IgG)

## IVIG: Historical Perspective

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- 1890-1910: *curative serum* (antitoxin prepared from animal sera) used to treat diseases caused by toxins, bacteria, allergies and cancers
- 1901 Von Berhing won the first Nobel Prize in Physiology and Medicine for his work on *serum therapy* : Rx of Diphtheria
- 1910-30: Serum sickness and anaphylaxis led to development and use of human convalescent serum in effort to prevent infections
- 1933-38: began to understand that antibodies were present in the globulin fraction of plasma

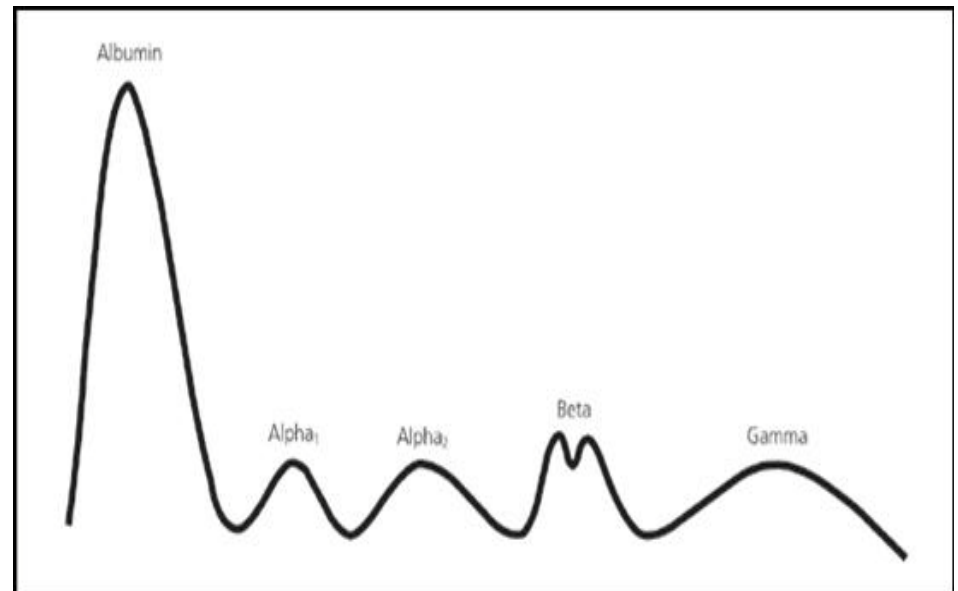
## IVIG : Historical Perspective

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- **1940s - new technology of protein electrophoresis and ethanol precipitation**
  - better separation and preparation
  - stable fractions
  - large scale fractionation for intravenous use
- **1950s - first use in the treatment of primary immunodeficiency (PID)**
- **1960s and 70s chemically and enzyme (pepsin) treated Ig**
  - Intravenous Ig superior to Intramuscular Ig
  - Contained only Fab fragments
  - Very short half life ( ~ 24 hours )

## Current Product : IVIG:

- Sterile liquid product
- Highly purified protein
  - ethanol fractionation
  - anion and cation exchange chromatography
- 98 % Ig G
  - Ig G subclasses
  - Ig A
  - Ig M
- Contains Fab and Fc portions



### **Plasma Derived (pooled) : potential disease transmission**

- **Screening and prevention against transmission:**
  - Donor selection
  - Testing of donors
  
- **Manufacturing and processing**
  
- **Pathogen removal/inactivation:**
  - solvent detergent
  - nano-filtration
  - heat inactivation

## Characteristics of Available Immune Globulin Products Licensed for Use in the UNITED STATES

BRAND NAME	Gammagard S/D		Gammagard Liquid	Carimune NF	Vivaglobin	Privigen	Flebogamma 5%	Flebogamma 5% DIF	Octagam	Gamunex
	5%	10%								
MANUFACTURER	Baxter Corporation/BioScience Division		Baxter Corporation/BioScience Division	CSL Behring	CSL Behring	CSL Behring	Grifols	Grifols	Octapharma	Talecris
METHOD OF PRODUCTION (Including Viral Inactivation)	Cohn-Onclay fractionation, ultra-filtration, ion-exchange chromatography, solvent detergent treatment		Cohn-Onclay fractionation, solvent/detergent treatment, ANX chromatography, 35nm nanofiltration, low pH/elevated temperature incubation	Kistler Nitschmann fractionation, pH 4.0, trace pepsin, nanofiltration	Cold alcohol fractionation, ethanol-latty alcohol/pH precipitation, pasteurization, diafiltered and ultrafiltered	Octanoic Acid Fractionation, CH9 Filtration, pH 4.0 incubation, Depth filtration, Chromatography, Nanofiltration	Cold alcohol fractionation, polyethylene glycol precipitation, ion exchange chromatography, pasteurization (60° C for 10 hours) and 8% PEG precipitation	Cold alcohol fractionation, polyethylene glycol precipitation, ion exchange chromatography, pH 4 treatment (4 hours at 37° C), pasteurization (60° C for 10 hours), solvent detergent treatment, and double sequential nanofiltration through 35 and 20 nm filters.	Cohn-Onclay cold ethanol fractionation, ultra-filtration, chromatography, solvent detergent treatment	Cohn-Onclay fractionation, caprylate/chromatography purification, cloth and depth filtration, final container low pH incubation
FORM	Lyophilized		Liquid	Lyophilized	Liquid	Liquid	Liquid	Liquid	Liquid	Liquid
SHELF-LIFE	24 Months		36 Months	24 Months	24 Months	24 Months (room temperature storage)	24 Months (room temperature storage)	24 Months (room temperature storage)	24 Months	36 Months
RECONSTITUTION TIME	<5 minutes at room temperature >20 minutes if cold		None (Liquid Solution)	Several Minutes	None (Liquid Solution)	None (Liquid Solution)	None (Liquid Solution)	None (Liquid Solution)	None (Liquid Solution)	None (Liquid Solution)
AVAILABLE CONCENTRATIONS	5%	10%	10%	3 to 12%	16% (160 mg protein/ per ml)	10%	5%	5%	5%	10%
MAXIMUM RECOMMENDED INFUSION RATE	4 mL/ kg/hour	8 mL/ kg/hour	5 mL/kg/hour	>2.5 mL/kg/hour	20 mL per hour	4.8mL/kg/hour	6.0 mL/kg/hour	6.0 mL/kg/hour	<4.2 mL/kg/hour	4.8 mL/kg/hour
*TIME TO INFUSE 35 gms	2.5 hours	0.6 hours	1 hour	<3.3 hours (6% Solution)	<sup>†</sup> Time will vary depending upon volume & tolerability	63 minutes	1.6 hours	1.6 hours	2.5 hours	1.0 hours
SUGAR CONTENT	20 mg/ml. glucose	40 mg/ml. glucose	No added sugars	1.67 gm sucrose per gram of protein	None	None	5% D-sorbitol (polyol)	5% D-sorbitol (polyol)	100 mg/ml. maltose	None
SODIUM CONTENT	8.5 mg/mL sodium chloride	17 mg/mL sodium chloride	No added sodium	<20 mg sodium chloride per gram of protein	3 mg/mL	Trace Amounts	<3.2 mmol/L	<3.2 mmol/L	≤30 mMol/L	Trace Amounts
OSMOLARITY/ OSMOLALITY	636 mOsm/L	1250 mOsm/L	240 - 300 mOsm/kg	192 - 1074 mOsm/kg	445 mOsm/kg	isotonic (320 mOsmol/kg)	240-350 mOsm/kg	240-370 mOsm/kg	310 - 380 mOsm/kg	258 mOsm/kg
PH	6.4 - 7.2		4.6 - 5.1	6.4 - 6.8	6.4 - 7.2	4.8	5.0 - 6.0	5.0 - 6.0	5.1 - 6.0	4.0 - 4.5
IgA CONTENT	< 2.2 µg/mL in a 5% solution		37 µg/mL	720 µg/mL	<1700 µg/mL	< or = 25mcg/mL	< 50 µg/mL	Average: < 3 mcg/mL (Specification value: < 50 mcg/mL)	<100 µg/mL	46 µg/mL
APPROVED METHOD OF ADMINISTRATION	Intravenous		Intravenous	Intravenous	Subcutaneous	Intravenous	Intravenous	Intravenous	Intravenous	Intravenous

<sup>1</sup>0.5 gm/kg for a 70 kg adult = 35 gms; 5% Concentrations: 1g = 20 mL; 10% Concentrations: 1g = 10 mL

<sup>2</sup>Time will vary depending upon volume and tolerability. Using 35 grams as monthly dose, calculate weekly dose=8.75 grams=55 mL infused into 4 sites @ site up to 20cch/site, which can range from 45 mins. To 3 hrs.

The time to infuse is based on the maximal infusion rate. Check product label for storage temperatures, which vary among Immunglobulin brands. Check package insert for detailed prescribing information.

Table updated August 2008.

- **Biphasic Decay**

**1<sup>st</sup> phase: rapid decay**

**immediate ↑ in Ig G levels followed by  
immediate equilibration with plasma Ig G**

**2<sup>nd</sup> phase: slower constant decay**

**1/2 life 18-25 days**

**(Half life is shortened in hypermetabolic states)**

## IVIg: Indications and Use

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- **Accepted approved clinical indications are limited to:**
  - **Primary Immunodeficiency**
  - **B cell leukemia with hypogammaglobulinemia**
  - **Kawasaki disease**
  - **GVHD post BMT**
  - **Pediatric AIDS**
  - **Immune Thrombocytopenia Purpura**

# IVIIG: Indications and Use

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- **60- 80 % of the use of IVIG is *off label***
- **Category Ia disease: Definite benefit**
  - **Chronic demyelinating neuropathies**
  - **Guillain Barré Syndrome**
  - **Neonatal Sepsis**
- **Category Ib II a and II b disease: Probably beneficial**
  - **Autoimmunity and immune complex diseases**
- **Category III - Might provide benefit**
- **Category IV - Unlikely to provide benefit**

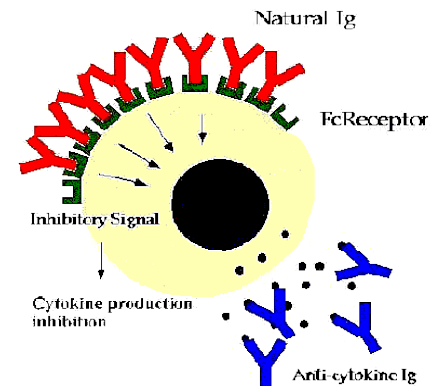
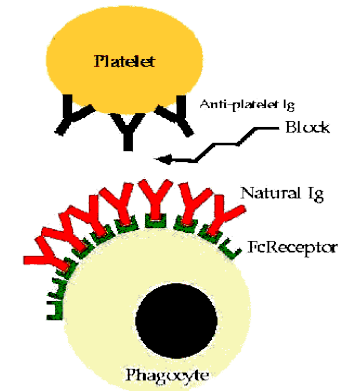
## Mechanism of action:

### Immunomodulatory Activity

- **Fc Receptor Blockade**
- **Ig binds activated complement components and inhibits their binding to the target cells**
- **Down modulation of autoantibody production**

### Modulation of Inflammation

- **Regulation of cytokine burst**
  - **Antibodies against cytokines**
  - **Induction of receptor antagonist**
- **Down modulation of T and B cell interaction cells**



### **Primary and Secondary Immunodeficiency**

**- 400mg/kg/ weekly (monthly)**

**Minimum serum level - 450 mg/dl**

**Replacement therapy goal : 960- 1120 mg/dl**

### **Immunomodulation:**

**Standard Dose : 1-2 Gm/Kg/day for 2-4 days**

## Adverse Events associated with IVIG

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- Generally occur during or immediately after infusion

### General

Fever  
Chills  
Headache/Flushing  
Anxiety/ Palpitations

### GI

Abdominal pain  
Nausea  
Vomiting

### Dermatologic

Urticaria  
Erythema Multiforme

### Respiratory

Wheezing  
Dyspnea  
SOB

### Cardiovascular

Tachycardia  
Hypotension  
Shock

### Hyperviscosity

\*Renal Insufficiency  
Thromboembolic events

Aseptic Meningitis

## Immunologic Reactions and Serologic Findings

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- **Allergic Reactions**
- **Anaphylactic Reactions**
- **TRALI**
- **Passive Sensitization**
- **Acute Hemolysis**

## IVIG and Ig A Deficiency

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- **Ig A is the most common of all Ig deficiencies (~ 1 in 700 Caucasians)**
- **Pathogenesis : block of the terminal differentiation of Ig A secreting B cells to plasma cells: Ig G and Ig M levels are normal/supernormal**
- **Severe anaphylactic reactions have been reported in patients with GI disease and Ig A deficiency**

### Factors to Consider

- **Ig A absent/deficient**
- **Anti Ig A**
  - **IgG or Ig E**
- **Concentration of Ig A in product**
- **Prior anaphylaxis**
- **Rate of infusion**
- **Alternative Rx:**
  - **Subcutaneous**
  - **SD plasma**
  - **Ig A Deficient Plasma**

## Transfusion Associated Lung Injury (TRALI) and IVIG

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- **A single case report**  
**23 year old with multifocal motor neuropathy received 90g IVIG**
- **Direct and indirect agglutination studies of the patient's serum was negative for HLA directed or granulocyte specific antibodies**
- **Indirect agglutination immunofluorescence studies (each lot ) reacted positively and detected surface bound immunoglobulin (broad reactivity) on the patient's granulocytes**
- **Persistently positive for several months suggesting that this may have been autoantibody rather than allo antibody from IVIG**

## Serologic Nuisances associated with IVIG

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- **Low titers of (Ig G) Anti A and Anti B have been found in all preparations**
- **Type O individuals with high titers**
- **Passive transfer of alloantibodies to red cell antigens**
  - **Interference with ABO and HLA typing**
  - **Positive Indirect Antiglobulin Test**
  - **Passive sensitization/positive DAT**

## IVIG Associated Hemolysis

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- **Although clinically significant hemolysis associated with IVIG is uncommon, hemolytic anemia requiring RBC transfusion can occur**
- **1980s- case reports of hemolytic transfusion reactions associated with IVIG**
- **1990s- several case series of IVIG associated hemolysis**

## IVIg Associated Hemolysis : Case Series I

### 38 patients

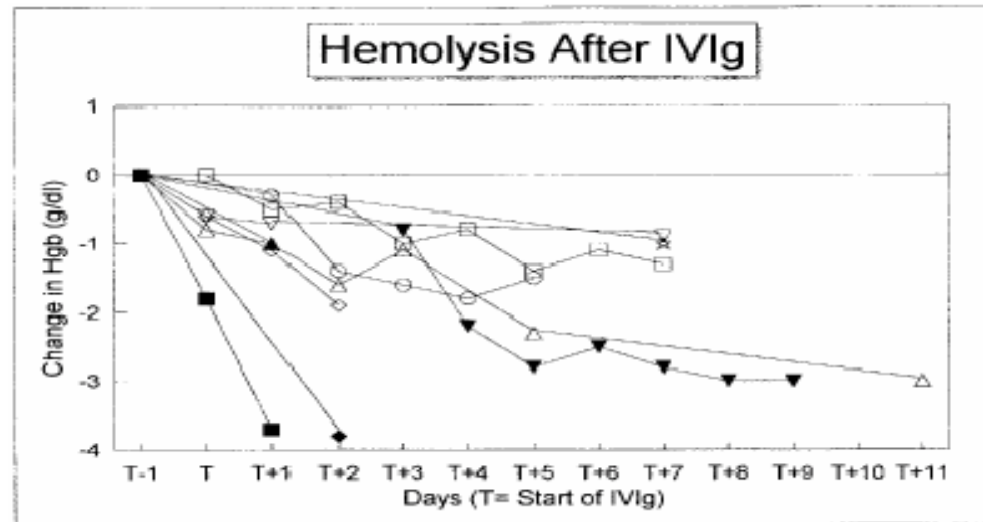
- 4 different lots
- single lot /pt
- 12/38 + DAT
- 5/12 hemolytic anemia
- 3/5 required TX

Patient	Indication	Blood type	Hgb pre-IVIg	Hgb post-IVIg	DAT	Antibody identified
1	Hypogammaglobulinemia	A+	15.6	11.9	+	Anti-A, anti-D
2	Myasthenia gravis	A+	14.0	10.2	+	Anti-A
3	Chronic lymphocytic leukemia (CLL) with hypogammaglobulinemia	A+	7.1	6.1	+	Anti-A, anti-D
4	CLL with idiopathic thrombocytopenic purpura	A+	8.4	6.8	+	Anti-A
5	Acute myelogenous leukemia with HSV infection	O+	8.8	6.7	+	Anti-D
6	CIDP	A+	12.2	9.3	+	Anti-A
7	CIDP	A+	15.5	14.1	+	Anti-A
8	CIDP	A+	8.6	6.7	+	Anti-A
9	GBS	A+	13.9	10.9	+	Anti-A
10	CIDP	A+	15.9	14.1	+	Anti-A
11	CIDP	A+	14.6	13.6	+	Anti-A
12	CIDP	A+	15.0	14.1	+	Anti-A

*Hgb, hemoglobin; HSV, herpes simplex virus.*

Wilson et al: *Muscle and Nerve* Sept 1997

## IVIg Associated Hemolysis: Case Series I



- **Timing and severity of hemolysis**
- **Nadir of Hb**

## Case series II: IVIG Associated Hemolysis

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- **16 patients**
- **Three different IVIG products**
  - **11/16 Gamunex**
  - **3/16 Gammagard**
  - **1/16 Combo**
- **Dose range: 50-350 g**
- **15/16 (94%) had evidence of hemolysis**
- **3/16 required RBCs TX**

Daw et al: *Transfusion* August 2008

## Case series II: IVIG Associated Hemolysis

### Serologic Findings

- 15/16 non Group O
- 14/16 (88%) +DAT (predominantly Ig G)
- 10/16 (63%) Anti A or Anti B in eluate/plasma

Case	Age (years), sex	Diagnosis	IVIG total amount (g)	Brand of IVIG	Blood group	DAT	Eluate and/or plasma	Decrease in Hb (g/L)	Hemolysis requiring RBC transfusion	Number of inflammatory markers*
1	27, F	Gestational ITP	50	Gammagard	AB-	Negative	Anti-A	14	No	1
2	50, F	Guillain-Barré syndrome	200	Gamunex	A+	Negative	ND	36	No	1
3	36, F	Sepsis ( <i>Streptococcus pyogenes</i> )	120	Gamunex	O-	Positive polyspecific	See text	43	Yes (2 units)	1
4	66, F	Guillain-Barré syndrome	100	Gamunex	AB+	Weak+ IgG	Negative	36	No	3
5	61, F	Postoperative necrotizing fasciitis	120	Gammagard	B+	1+ IgG	Anti-B	†	No	4
6	51, F	Postoperative necrotizing fasciitis	100	Gamunex	A+	Weak+ IgG, 1+ complement	Anti-A	32	No	4
7	44, F	HIV+, CAH, sepsis	315	Gamunex + Gammagard	B+	Weak+ IgG	Anti-B	34	No	6
8	71, M	Rhabdomyolysis	200	Gamunex	A+	Weak+ IgG	Anti-A	30	No	1
9	19, F	Viral meningitis with postinfectious Guillain-Barré syndrome	180	Gamunex	A+	Weak+ IgG	Anti-A	47	No	1
10	23, F	ITP	210	Gamunex	B+	Weak+ IgG	Anti-B	51	No	0
11	60, M	Guillain-Barré syndrome	200	Gamunex	A+	Weak+ IgG	Anti-A	50	No	2
12	18, F	Viral encephalitis	120	Gamunex	B+	Weak+ IgG	Negative	24	Yes (1 unit)	3
13	60, M	Postoperative necrotizing fasciitis	350	IGIVnex	A+	3+ IgG	Anti-A	8	No	1
14	55, M	Guillain-Barré syndrome	300	Gammagard	B+	Weak+ IgG	Negative	52	No	2
15	22, M	Systemic lupus	285	Gamunex	B+	Weak+ IgG	Auto‡	13	Yes (3 units)	4
16	49, M	Guillain-Barré syndrome	295	Gamunex	A+	1+ IgG	Anti-A	30	No	3

\* Inflammatory markers include haptoglobin, ferritin, fibrinogen, D-dimer, erythrocyte sedimentation rate, C-reactive protein, or decreased serum albumin.  
† Ongoing RBC transfusions resulted in an increase of 19 g per L, but this increment is less than expected.  
‡ Eluate demonstrated warm auto-antibodies.  
CAH = cold agglutinin hemolysis; ITP = immune thrombocytopenic purpura; ND = not done.

## Case Series II: IVIG Related Hemolysis

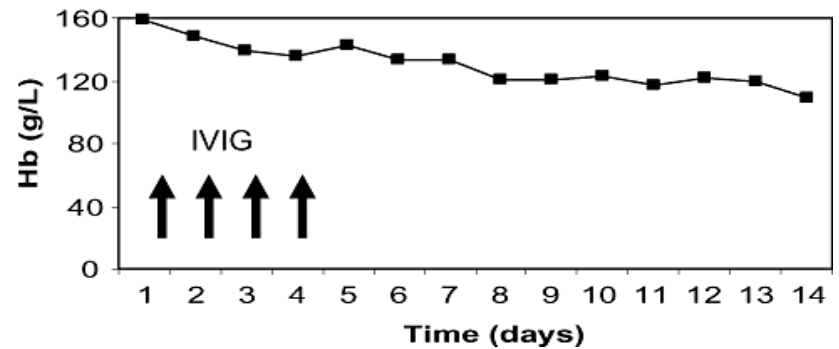
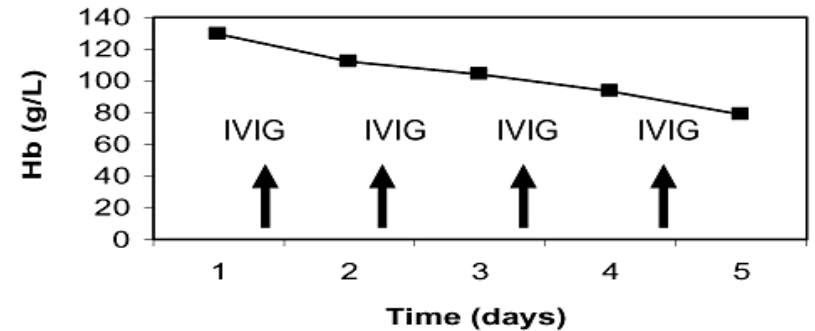
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### Serologic Findings

- **Positive DAT were mostly weak Ig G**
  - 1 case DAT 3+
  - 1 case + complement (TX of RBC and FFP)
- **6/10 cases had major co-morbidities**
- ***in vitro* testing of the Group O patient's RBCs with IVIG resulted in hemolysis**

## Case Series II: IVIG Related Hemolysis

- Timing of hemolysis
- Hb Nadir after 1<sup>st</sup> dose
  - Patient with ITP
  - Patient with GBS



## Factors associated with IVIG related hemolysis

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- **High cumulative dose**
- **Non-O blood type**
- **Female 63% (10/16)**
- **Positive serologic marker of inflammation was present in 94% (15/16) of patients**

## Possible Etiologies: IVIG Associated Hemolytic Reactions

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- **Passive transfer of ABO isohemagglutinin**
- **Soluble ABO blood group substance**
- **Pre-primed immune systems and complement activation**
- **Passive sensitization with Ig G subclasses (1 and 3) that fix complement**
- **Underlying Inflammatory state - enhance removal of the sensitized RBCs**

# Summary

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- **Benefits of IVIG therapy include anti-inflammatory and immunomodulatory effects**
- **Adverse events associated with IVIG are generally allergic type reactions or related to rate of the infusion**
- **Patients who are Ig A deficient may require extra caution**
- **Clinicians should be aware of the potential serious complication of IVIG associated hemolysis**
- **Transfusion Medicine Services should be mindful of the serological nuisance that can occur after administration of IVIG**

# Conclusion

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## **Proposed management of patients with IVIG associated hemolysis:**

- **Vary the lots of products used**
- **XM**
- **Dose algorithms based on titer of the antibodies in the product**
- **Pre test all patients receiving IVIG:**
  - **ABO/Rh, DAT (eluate if +) , CBC, LDH and Bilirubin**
  - **Post testing at 36 hrs**
- **Special consideration for female patients**